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The nitroolefinic behaviour of 4-nitrobenzodifuroxan

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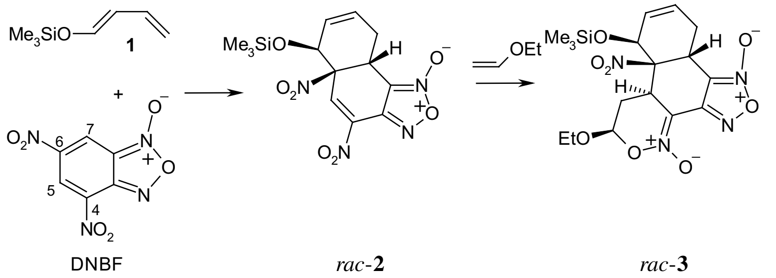
Abstract—4-Nitrobenzodifuroxan (NBDF) is shown to possess a nitro-activated double bond of 1.339 Å, which exhibits a high reactivity both in normal and inverse electron demand Diels–Alder condensations. NBDF is also shown to react as a Michael acceptor. Altogether, the results reveal that the nitroolefinic character of NBDF is considerably higher than that of 4,6-dinitrobenzofuroxan.

The high susceptibility of nitrobenzofurazans and related 1-oxides, that is, nitrobenzofuroxans, to undergo covalent addition or substitution processes has attracted considerable attention in the last two decades, leading to numerous synthetic, analytical and biological applications.[1–9] Prototype examples of this behaviour are the facile carbon–carbon coupling reactions of 4,6-dinitrobenzofuroxan (DNBF)—the reference compound in the series—with a number of benzenoid aromatics (phenols, anilines)[2,3] or π-excessive heteroaromatics (indoles, pyrroles, thiophenes)[10] whose carbon basicities are associated with large negative pK_a values (up to −10), for example, p$K_a = -3.46$ for protonation of indole at C-3.[10c] From detailed kinetic studies of these reactions, it has been shown that DNBF is a stronger electrophile than the 4-nitrobenzenediazonium cation.[10a]

In accord with the idea that the low aromatic character of the benzofuroxan or benzofurazan structures is a major factor responsible for the exceptional electrophilic reactivity of DNBF and related heterocycles,[1a] recent studies have revealed that nitrobenzofuroxans and not benzofurozans are very versatile Diels–Alder reagents.[11,12] An illustrative example is given in Scheme 1, which shows that the reaction of DNBF with 1-trimethylsilyloxybuta-1,3-diene **1** proceeds with high



Scheme 1.

Keywords: Nitrobenzofuroxan; Nitroalkenes; Diels–Alder cycloadditions; Michael additions.

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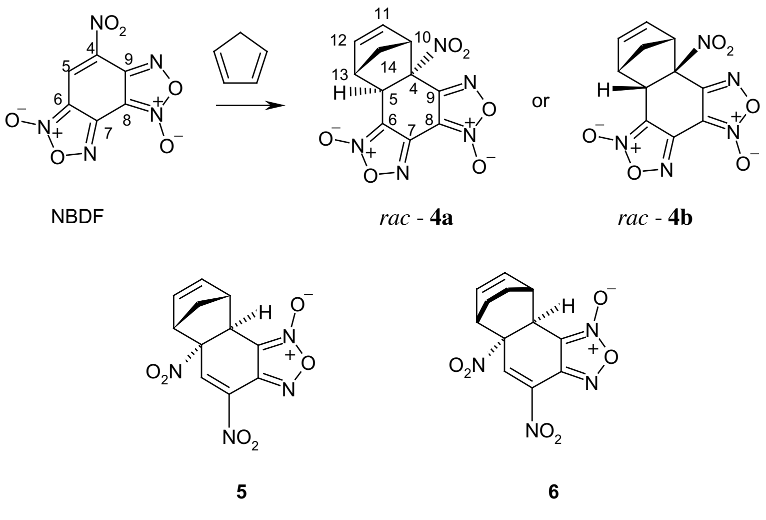
endo stereoselectivity as well as high regioselectivity, giving rise to the monoadduct **2** nearly quantitatively.[11b] Interestingly, this adduct was inert to further reaction with **1** but not with vinyl ethyl ether. Thus, the dihydrooxazine N-oxide **3** was obtained in 90% yield resulting from a highly diastereoselective inverse electron demand Diels–Alder (IDA) addition involving the O4–N4–C4–C5 fragment of **2** as the heterodiene contributor. Adducts arising from two successive and stereoselective normal Diels–Alder (NDA) or inverse electron-demand cycloadditions have been characterized in other systems.[11a,12–15] Other important reactivity patterns refer to the behavior of the carbocyclic ring as a 1,3-diene,[12] the heterodiene behavior of the annelated five-membered ring,[13b] as well as the dienophilic contribution of the NO groups of the *ortho*-dinitroso intermediates involved in the typical 1-oxide/3-oxide tautomerism of benzofuroxans.[13b,16] Altogether, the above results have revealed that the overall pericyclic reactivity of DNBF and related heterocycles is largely related to that of nitroolefins.[17–20]

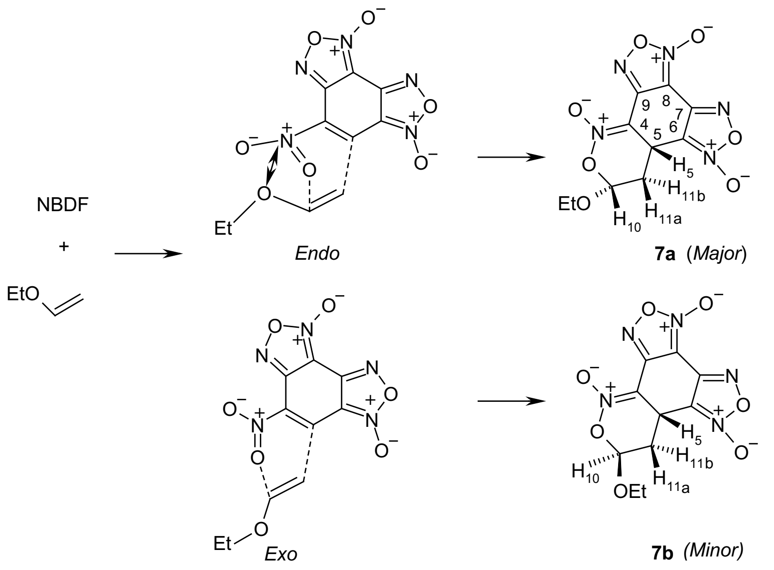
On this basis, we became interested in establishing whether this type of reactivity will extend to related structures such as 4-nitrobenzodifuroxan (NBDF). Our interest in NBDF was stimulated by our finding that the nitroactivated C4–C5 double bond of this compound is olefinic in nature with a length of 1.339 Å.[21] This is in marked contrast with the situation reported for DNBF where values of 1.37 and 1.40 Å have been measured for the most reactive double bond C6–C7 and the most aromatic double bond C4–C5, respectively.[22] In accord with these data, we report that NBDF is considerably more reactive than DNBF both in NDA and IDA processes. Also, NBDF is found to react as a Michael acceptor, a behavior which represents a new reactivity pattern in benzofuroxan chemistry.

Treatment of NBDF with excess cyclopentadiene (10 equiv)[23] in chloroform for 2 h at room temperature resulted in the formation of a solid, which was readily isolated as white crystals in good yield (76%). Analysis of the ^1H and ^{13}C NMR spectra of the product recorded in Me_2SO-d_6 led to its identification as the cycloadduct **4a** and not the diastereomer **4b** (in their racemic forms)[23] resulting from a diastereoselective NDA process involving the C4–C5 double bond of NBDF as the dienophile component (Scheme 2). Major diagnostic features of the condensation process were the disappearance of the low-field proton typical of the olefinic moiety of NBDF and the strong deshielding of the sp^3 carbon C4 in the resulting adduct. This carbon benefits from the strong electron-withdrawing inductive effects exerted by both the NO_2 group and the adjacent furoxan ring.[24] The X-ray structure, which was obtained agreed with the formation of **4a**.[21] The *endo* configuration of **4a** with the 4-NO_2 group and H5 being in a *trans* arrangement to the C13–C14–C10 bridge compares well with that established for the corresponding DNBF-cyclopentadiene and -cyclohexadiene adducts **5** and **6**.[12a,25] As a consequence of the strong nitroolefinic character of NBDF, **4a** is formed considerably faster than **5** (5 days at 0 °C) or **6** (*ca.* 7 days at room temperature).[12a]

Reaction of NBDF with an excess of ethyl vinyl ether under the same experimental conditions as used in Scheme 2 rapidly produced a white solid, which was isolated in 80% yield.[26] Examination of the ^1H and ^{13}C NMR spectra recorded after dissolution of this solid in acetone-d_6 revealed a mixture of the two diastereomeric dihydrooxazine 1-oxides **7a** and **7b** in a 95:5 ratio (only one enantiomer of each is shown in Scheme 3).[26] Consistent with these structures was the observation in the ^1H NMR spectra of both **7a** and **7b** of well-defined AMXY systems in which the AMX part reflects the coupling of the nonequivalent methylenic protons H11a and H11b with H5 of the carbocyclic ring: $\delta_{H11a} = 3.48$; $\delta_{H11b} = 2.16$; $^3J_{H5\text{–}H11a} = 5.9$; $^3J_{H5\text{–}H11b} = 12.5$ for **7a**; $\delta_{H11a} = 3.03$; $\delta_{H11b} = 2.53$; $^3J_{H5\text{–}H11a} = 5.2$; $^3J_{H5\text{–}H11b} = 12.5$ for **7b**. Interestingly, irradiation of the most deshielded H11a proton of **7a** caused notable changes in the intensity of both the H5 and H10 resonances, indicating that these three protons are located on the same side of the dihydrooxazine 1-oxide ring. The situation compares well with that found in the DNBF–ethyl vinyl ether



Scheme 2.



Scheme 3.

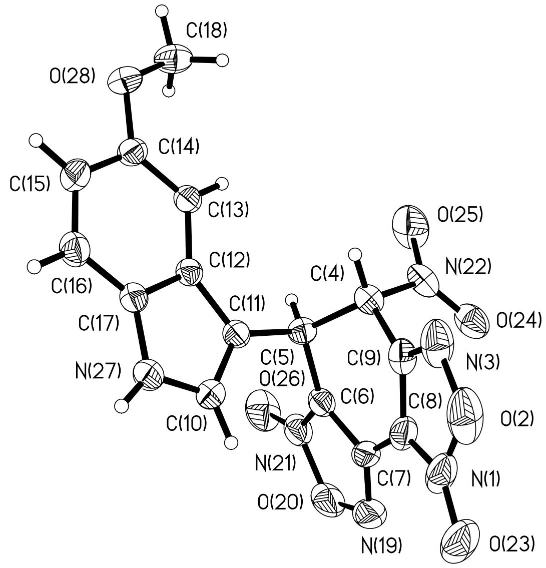
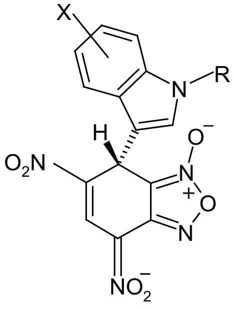


Figure 1. X-ray structure of compound **9**.

system where the two cycloadducts arising from the *endo* and *exo* approaches were obtained in a 4:1 ratio, respectively.[11a] As borne out by a theoretical study,[27] the predominant formation of the *endo* product in this system is the result of a possible stabilisation of the related transition state by a secondary orbital interaction between the oxygen atom of the enol ether and the nitrogen atom of the nitro group involved in the heterodienic moiety. As depicted in Scheme 3 it is reasonable to anticipate a similar preferential stabilisation of the *endo* transition state leading to **7a** in the NBDF–ethyl vinyl ether interaction.

Besides the high reactivity exhibited in Schemes 2 and 3, a major feature illustrating the nitroolefinic character of NBDF is the ability of this compound to act as a Michael acceptor. In contrast to DNBF, which reacts with indoles to afford exclusively sigma-adducts of type **8** through a formal S_EAr substitution of the indole ring,[10] NBDF reacts with 5-methoxyindole to give the adduct **9**.[28] As shown by the crystal structure for **9** in Figure 1,[29] the reaction proceeds with bonding of the C-5 carbon of NBDF to the C_β position of the indole moiety. This behavior of NBDF is reminiscent of that of nitroalkenes, which are well known to couple with indole nucleophiles in Michael-type reactions.[30,31] No evidence for the occurrence of an IDA process where NBDF would act as a heterodiene and the indole molecule as a dienophile has been found.[32]



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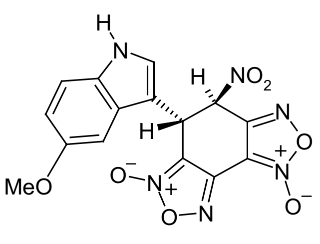

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In conclusion, the reactivity patterns of NBDF add to the versatile behavior of nitrobenzofuroxans while providing further evidence that this versatility is largely related to the olefinic character of the nitroactivated double bonds.

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23. Preparation of **4a**. Excess cyclopentadiene (10 equiv) was added to a suspension of 0.2 g (0.84 mmol) of NBDF[33] in $CHCl_3$ (10 mL) at room temperature and the reaction mixture stirred at this temperature for 2 h. The resulting white precipitate was collected by filtration, washed with chloroform and dried under vacuum. The adduct **4a** was then obtained in 76% yield. Crystals of **4a** were obtained by recrystallization from methanol. Selected data for **4a**: mp 194 °C (dec); *m/z* (EI) 262 $(M{+}H{-}N_2O)^+$, 200 $(M{+}H{-}NO_2, -N_2O_2)^+$; ^1H NMR (300 MHz, DMSO-d_6) δ 1.69 (d, $J = 10.6$ Hz, 1H, H-14a), 1.79 (d, $J = 10.6$ Hz, 1H, H-14b), 3.48 (s, 1H, H-13), 4.03 (m, 1H, H-10), 4.04 (m, 1H, H-5), 6.31 (dd, $J = 5.3$, 2.6 Hz, 1H, H-12), 6.84 (dd, $J = 5.3$, 3.1 Hz, 1H, H-11); ^{13}C NMR (75 MHz, DMSO-d_6) δ 42.71 (C-14), 46.55 (C-13), 47.83 (C-5), 57.46 (C-14), 92.96 (C-4), 105.73 (C-8), 111.51 (C-6), 134.53 (C-12), 142.50 (C-11), 142.72 (C-7), 152.83 (C-9). Anal. Found: C, 43.71; H, 2.35; N, 22.40. $C_{11}H_7N_5O_6$ requires: C, 43.29; H, 2.31; N, 22.95.
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26. Preparation of **7**. Using the same experimental conditions as for **4a**, the dihydrooxazine 1-oxide **7** was collected as a white solid consisting of the two diastereomers **7a** and **7b** in a 95:5 ratio (see text). The reaction proceeds in 80% yield. Selected data for **7a**,**b**: mp (mixture) 163 °C (dec); HRMS (EI) calcd for $C_{10}H_{10}N_5O_7$ $(M{+}1)^+$ 312.2195, found 312.2189; ^1H NMR **7a** (300 MHz, acetone-d_6) δ 1.21 (t, $J = 7.0$ Hz, 3H, CH_3), 2.16 (ddd, $J = 13.0$, 12.5, 4.4 Hz, 1H, H-11b), 3.48 (ddd, $J = 13.0$, 7.5, 5.9 Hz, 1H, H-11a), 3.78 (dq, $J = 14.0$, 7.0 Hz, 1H, CH_2), 4.02 (dq, $J = 14.0$, 7.0 Hz, 1H, CH_2), 4.56 (dd, $J = 12.5$, 5.9 Hz, 1H, H-5), 5.96 (dd, $J = 7.5$, 4.4 Hz, 1H, H-10); ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.90 (CH_3), 30.32 (C-5), 32.08 (C-11), 66.12 (CH_2), 103.78 (C-8), 104.35 (C-6), 106.09 (C-10), 113.27 (C-4), 140.07 (C-7), 150.81 (C-9); ^1H NMR **7b** (300 MHz, acetone-d_6) δ 1.21 (t, $J = 7.0$ Hz, 3H, OCH_3), 2.53 (ddd, $J = 13.3$, 12.5, 3.3 Hz, 1H, H-11b), 3.03 (ddd, $J = 13.3$, 5.2, 2.6 Hz, 1H, H-11a), 3.87 (dq, $J = 14.0$, 7.0 Hz, 1H, CH_2), 4.02 (dq, $J = 14.0$, 7.0 Hz, 1H, CH_2), 4.93 (dd, $J = 12.5$, 5.2 Hz, 1H, H-5), 5.91 (dd, $J = 3.3$, 2.6 Hz, 1H, H-10).
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28. Preparation of **9**: 31 mg (0.21 mmol) of 5-methoxyindole were added to a solution of 50 mg (0.21 mmol) of NBDF in 3 ml of ethyl acetate at room temperature. The resulting mixture was stirred and heated to reflux for 1 min. After removal of the solvent under vacuum, the residue was dissolved in diethyl ether (10 mL) and the solution was filtered. Addition of pentane (50 mL) resulted in the precipitation of **9**, which was dried under vacuum (yield: 59%) and recrystallised from diethyl ether. Selected data for **9**: mp 127 °C (dec); *m/z* (EI) 195 $(M{+}H{-}NO_2{-}(MeO{-}indole))^+$; ^1H NMR (300 MHz, CD_3CN) δ 3.85 (s, 3H, OCH_3), 5.94 (dd, $J = 2.2$, 0.9 Hz, 1H, H-5), 6.82 (d, $J = 2.2$ Hz, 1H, H-4), 6.89 (dd, $J = 8.9$, 2.2 Hz, 1H, H-15), 7.26 (d, $J = 2.6$ Hz, 1H, H-10), 7.37 (d, $J = 8.9$ Hz, 1H, H-16), 7.41 (d, $J = 2.2$ Hz, 1H, H-13), 10.45 (br, 1H, NH); ^{13}C NMR (75 MHz, CD_3CN) δ 35.16 (C-5), 56.82 (OCH_3), 81.33 (C-4), 101.23 (C-13), 101.89 (C-15), 105.90 (C-8), 114.16 (C-6), 114.43 (C-11), 114.73 (C-16), 126.19 (C-12), 128.36 (C-10), 133.05 (C-17), 146.98 (C-7), 149.38 (C-9), 156.25 (C-14).
29. X-ray crystallographic data of **9**: $C_{19}H_{20}N_6O_8$, FW = 460.41 g mol^{-1}, triclinic, P-1, $a = 7.3530(1)$ Å, $b = 11.2191(2)$ Å, $c = 14.1954(2)$ Å, $\alpha = 104.310(2)°$, $\beta = 103.215(1)°$, $\gamma = 92.723(1)°$, $V = 1097.92(3)$ Å^3, $D_{calcd} = 1.393$ g cm^{-3}, $Z = 4$, $\mu(MoK\alpha) = 0.111$ mm^{-1}, no of measured reflections 5118, no of reflections with $I > 2\sigma(I)$ 3137, parameters = 302, $R_1 = 0.0710$, $wR_2 = 0.1745$ (all). X-ray data for the adduct **9** were collected on a three-circle diffractometer equipped with a bidimensional CCD detector. The crystal structure (Fig. 1) has been deposited at the Cambridge Crystallographic Data

Centre and allocated the deposition number CCDC-222455.

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